REMARKS

Applicants respectfully request entry of the foregoing and reconsideration of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. §1.116, and in light of the remarks that follow.

Claims 5-14, 16-25, 27-37 and 39-47 are pending in the application.

By the above amendments, claims 5, 39, 40, 43 and 44 have been amended to further clarify that the polymer associate defined in these claims includes at least one of a monoacyl phospholipid, a diacyl phospholipid and a mixture of monoacyl and diacyl phospholipids. Also, claims 31 and 32 are amended to include proper Markush group language and to be consistent with other claims in the application.

Applicants thank the Examiner for acknowledging the Request for Extension of Time and the Amendment filed on January 27, 2003.

Turning now to the Official Action, claims 5 and 6 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants have amended claim 5 to obviate this rejection. In particular, Applicants have amended claim 5 to read, in part, "...wherein the monoacyl phospholipid, or the mixture of monoacyl and diacyl phospholipids are obtained by enzyme digestion of lecithin. Applicants submit that this amendment addresses the issue raised with respect to the term "the diacyl phospholipid."

Applicants respectfully request reconsideration and withdrawal of the §112, second paragraph, rejection of claims 5 and 6.

Claims 5, 7-14, 16-19, 31-39, 42-43 and 46-47 stand rejected under 35 U.S.C. §102(b) as being anticipated by *Leigh* (U.S. Patent No. 5,141,674). For at least the reasons that follow, withdrawal of the rejection is in order.

First, Applicants note that claim 38 was canceled by the Amendment filed on January 27, 2003. Thus, Applicants have not provided remarks with respect to the rejection of claim 38.

Exemplary embodiments of the present invention relate to the preparation of powder or solid compositions comprising single and double chain amphiphilic lipids generally. Lipid compositions comprising monoacyl and diacyl membrane lipids are associated with polymers and biologically active compounds for administration to a living organism. Lipid polymer compositions can be produced which have improved physical characteristics and higher loading capacity for lipophilic and hydrophilic compounds. Stable membrane lipid compositions in particulate and in compact forms can be produced with superior bio availability, suitable for oral and other applications. See specification at page 1, lines 5-15.

For example, claim 39, as amended above, defines a phospholipid polymer associate prepared by removing an organic solvent or an organic solvent and water from a solution comprising (i) at least one of a monoacyl phospholipid, a diacyl phospholipid and a mixture of monoacyl and diacyl phospholipids; (ii) a polymeric material; and (iii) an organic solvent or a mixture of an organic solvent and water, the phospholipid polymer associate being of particulate form.

Also, claim 43, as amended above, defines a method of preparing a phospholipid polymer associate, the method comprising (i) forming a solution by combining at least one of a monoacyl phospholipid, a diacyl phospholipid and a mixture of monoacyl and diacyl phospholipids with a polymeric material and an organic solvent or a mixture of an organic solvent and water; and (ii) removing the organic solvent or mixture of the organic solvent and water so that the resulting phospholipid polymer associate is in particulate form.

Also, independent claim 31, as amended above, defines a lipid composition for administration to a living organism, the composition comprising a biologically active compound and a lipid selected from the group consisting of a monoacyl phospholipid, a diacyl phospholipid and a mixture of monoacyl and diacyl phospholipids.

Leigh relates primarily to a composition based on a membrane lipid and at least one biologically active compound in the form of a micronized powder and to a method of making a progenator of liposomes or pro-liposome in the form of an aerosol or discreet particles.

It is well established that in order to demonstrate anticipation under §102(b), each element of the claim in issue must be found, either expressly described or under principles of inherency, in a single prior art reference. See Kalman v. Kimberly-Clark Corp., 218 U.S.P.Q. 789 (Fed. Cir. 1983). That is not the case here.

For example, at column 4, lines 19-25, *Leigh* explains that the composition disclosed therein is a powder composition comprising a uniform mixture of solid particles whose major component is a physiologically-acceptable solid carrier and whose minor component is the biologically active compound in particulate dispersion in the lipid. Thus,

Applicants submit that the composition of *Leigh* includes a major component which is a polymer (e.g., starch, dextran etc.) or sugar (e.g., lactose) that is insoluble in the solvent (prior to evaporation). A second component is then used as an inert diluent or bulking agent to carry the drug-lipid particles so that they can be filled into capsules and dispensed from a dry powder inhaler. See *Leigh* at column 4, lines 1-4. The composition also includes a minor component, which includes micronized drug particles dispersed in phospholipids.

In stark contrast to the teachings of *Leigh*, however, the polymer associate defined in claims 39 and 43 and the composition of claim 31 are made with lipid associates wherein the particles each comprise drug/lipid/polymer. In other words, the components in the polymer associate are distributed in a substantially uniform manner throughout the particulate lipid associates. This is achieved by putting the drug/lipid/polymer into solution prior to solvent removal to form the lipid associates.

Furthermore, the polymer associate of claim 40 and the method of preparing a polymer associate according to claim 44 are distinguished from *Leigh* in that *Leigh* fails to disclose or suggest a particulate phospholipid polymer associate prepared by removing water from a homogeneous dispersion comprising (i) at least one of a monoacyl phospholipid, a diacyl phospholipid and a mixture of monoacyl and diacyl phospholipids; (ii) a natural polysaccharide; and (iii) water.

For at least these reasons, claims 31, 39, 40, 43 and 44 are patentable over *Leigh*. In addition, because claims 5, 7-14, 16-19, 32-37, 42, 46 and 47, depend directly or indirectly, from these claims, claims 5, 7-14, 16-19, 32-37, 42, 46 and 47 necessarily

include all of the limitations of independent claims 31, 39, 40, 43 and 44 and are therefore patentable over *Leigh* for at least the reasons that claims 31, 39, 40, 43 and 44 are patentable thereover. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 5-14, 16-19, 31-39, 42-43 and 46-47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Leigh* in view of *Huang* (U.S. Patent No. 5,043,164), *Baumann* (U.S. Patent No. 5,009,956) individually or in combination. For at least the reasons that follow, withdrawal of the rejection is in order.

As claim 38 hs been canceled by a previous Amendment, Applicants do not address the rejection of claim 38.

With respect to *Leigh* Applicants submit that for at least all of the reasons set forth above with respect to the §102(b) rejection of claims 5, 7-4, 16-19, 31-39, 42, 43, and 46-47, claims 5-14, 16-19, 31-37, 39, 42-43 and 46-47 also would not have been obvious over *Leigh.*

In particular, in order to establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. See In re Royka, 490F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In addition, "all words in a claim must be considered in judging the patentability of that claim against the prior art." See In re Wilson, 424F.2d 1382, 1385; 165 U.S.P.Q. 494, 496 (CCPA 1970). See MPEP §2143.03.

As explained above, however, *Leigh* does not disclose or fairly suggest all of the claim limitations of claims 31, 39, 40, 43 and 44. Specifically, *Leigh* does not disclose or

fairly suggest the phospholipid polymer associate of claims 31, 39 or 43 because *Leigh* discloses a polymer that is insoluble in solvent. That is, Applicants submit that the powder of *Leigh* does not include a substantially uniformly distributed quantity of drug, lipid and polymer. In addition, *Leigh* does not disclose or fairly suggest a polymer associate prepared by removing water from a homogeneous dispersion comprising at least one monoacyl phospholipid, a diacyl phospholipid and a mixture of monoacyl and diacyl phospholipids, a natural polysaccharide and water, as set forth in independent claims 40 and 44.

None of the cited secondary references overcome the above deficiencies of *Leigh*. In this regard, Applicants respectfully submit that the reliance on these secondary references is improper because the rejection relies only on specific elements of the subject matter disclosed therein, which is taken out of context and disregards the overall teachings of the secondary references. In particular, it has been established that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to are of ordinary skill in the art." See In re Wesslau, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (CCPA 1965); and Bausch & Lomb, Inc. v. Barnes-Hind, 796 F.2d 443, 448-49, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986) (holding that district court, by failing to consider a prior art reference in its entirety, ignored portions of the reference).

For example, *Baumann* is substantially directed to *in vivo* stabilization of liposomes in serum. See *Baumann*, for example, at column 2, lines 9-12 and column 3, lines 10-21.

In particular, *Baumann* discusses using lysolecithins to prevent the cleavage of liposomes by phospholipiase A, which is present in serum after intravenous administration. See *Baumann*, for example, at column 2, lines 9-33.

Additionally, *Huang* is substantially directed to using lysophospholipds to stabilize liposomes to be resistant against the lytic action of albumin (a major blood component). See *Huang* for example at column 2, lines 44-48. Thus, *Huang*, like *Baumann*, is concerned with intravenous administration. In contrast, however, the present invention does not include phospholipase. Thus, even if *Huang* and/or *Baumann* were combined with *Leigh*, one would not arrive at the invention of independent claims 39, 40, 43 and 44.

Additionally, while the secondary references are related to intravenous administration, the present invention is substantially related to oral administration. Thus, one of ordinary skill in the art would not have even been motivated to consider the possibility of combining stabilization mechanisms specific to intravenous routes of administration with a delivery system intended for oral administration because the requirements of these two routes of administration are entirely different from a physiological standpoint.

Furthermore, the asserted combination of *Leigh* in view of *Baumann* and/or *Huang* ignores the teaching of the prior art, which Applicants believe actually teaches away from making the asserted combination. That is, the asserted combination of references ignores the teachings of *Morris et al.*, "Interaction of Lysophosphatidylcholines With Phosphatidylcholine Bilayers," Biochimica et Biophysica Acta 599 (1980), pages 380 to 390 (summary page 380, lines 3-4; introduction page 381, second paragraph, lines 1-4;

page 386, lines 3-4 and Figure 5; conclusions page 388, lines 1-11; and page 388 third paragraph last line to page 389, line 2), and *van Echteld et al.*, "Effects of Lysophosphatidylcholines on Phosphatidylcholines and Phosphatidylcholine/Cholesterol Liposome Systems as Revealed by P-NMR, Electron Microscopy and Permeability Studies," Biochemica and Biophisica Acta, 649 (1981), pages 211-220 (Abstract/Summary page 211, lines 13-15; Introduction page 211, right column, line 3- page 2212, left column, line 2; page 217, section 4 "Permeability changes," whole section, Figs. 6 and 7, which clearly disclose that lysolecithin and lyso-components are known to de-stabilize liposomes. Thus, one of ordinary skill in the art would also not have been motivated to combine *Leigh* with *Baumann* and/or *Huang* for this reason. For the Examiner's convenience, copies of *Morris et al.* and *van Echteld et al.* are attached hereto.

For at least these reasons, claims 31, 39, 40, 43 and 44 are patentable over *Leigh*, *Baumann* and *Huang*, separately or in combination. Also, because claims 5-14, 16-19, 32-37, 42 and 46-47 all depend, directly or indirectly, from claims 31, 39, 40, 43 and 44, these claims are also patentable over *Leigh*, *Bauman* and *Huang* for at least the reasons that claims 31, 39, 40, 43 and 44 are patentable thereover. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 5-14, 16-25, 27-37 and 39-47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over JP 7291854 in view of *Huang* and *Baumann* individually or in combination. For at least the reasons that follow, withdrawal of the rejection is in order.

JP '854 is directed to a composition comprising a sparingly soluble drug, a hydrophilic polymer and a solubilizing agent in the presence of a aqueous solvent, which is

removed. The solubilizing agent is preferably a polyhydric alcohol, polyhydric alcohol ether or ester, or lecithin. The composition is obtained by adding the hydrophilic polymer and the solubilizing agent to a sparingly soluble drug, pulverizing the resultant mixture in the presence of an aqueous solvent in an amount so as not to completely dissolve the sparingly soluble drug, then removing the aqueous solvent by drying etc., and providing a solid dispersion.

From the Abstract of JP '854, Applicants submit that it is apparent that JP '854 fails to render obvious claims 31, 39, 40, 43 or 44. That is, JP '854 fails to disclose or fairly suggest drug/lipid/polymer in co-solution in an organic solvent or a mixture of an organic solvent and water. Additionally, JP '854 fails to disclose or suggest that these components are in a homogeneous co-dispersion in water prior to removal of the water. In fact, the Abstract of JP '854 as provided by the Patent Abstracts from the Japanese Patent Office fails to even teach lecithin. For the Examiner's convenience, Applicants have provided a copy of the Abstract of JP '854 from the Japanese Patent Office.

Huang and *Baumann* fail to overcome the deficiencies of JP '854. That is, for at least the reasons set forth above, Applicants believe that *Huang* and *Baumann* are again substantially different from JP '854 so that one of ordinary skill in the art would not have been motivated to combine these references with JP '854. Moreover, Applicants believe that even if combined, one would not arrive at the invention of claims 31, 39, 40, 43 or 44.

For at least these reasons, the invention of claims 31, 39, 40, 43 and 44 would not have been obvious over JP '854, *Baumann* or *Huang*, either separately or in combination.

As the remaining rejected claims depend directly from claims 31, 39, 40, 43 and 44, these remaining claims are patentable over JP '854, *Baumann* and *Huang* for at least the reasons that claims 31, 39, 40, 43 and 44 are patentable thereover. Applicants respectfully request reconsideration and withdrawal of the rejection.

From the foregoing, Applicants earnestly solicit further and favorable action in the form of a Notice of Allowance.

If there are any questions concerning this paper or the application in general, Applicants invite the Examiner to telephone the undersigned at the Examiner's earliest convenience.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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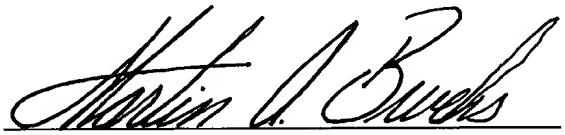
By: 

Martin A. Bruehs
Registration No. 45,635

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Attachments:
Morris et al., BBA, 599 (1980) pages 380-390
van Echteld et al., BBA 649 (1980) pages 211-220
Japanese 07291854 (Patent Abstracts of Japan)